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Study of BDNF-TrKB Trafficking Regulated by Neuronal Activity in Hippocampal Neurons by Live Cell Imaging
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Brain-derived neurotrophic factor (BDNF) is a protein that regulates neuronal survival and synaptic plasticity in brain. BDNF binds and activates receptor tyrosine kinase TrkB and the trafficking of phosphorylated TrkB triggers multiple intracellular pathways involved in neuronal development. It is not clear, however, whether BDNF is transported with TrkB in a signaling complex.
It has been reported that the number of surface TrkB and the phosporylation of TrkB is enhanced by high frequency neuronal activity, but whether the trafficking of TrkB is also modulated by neuronal activity has not been addressed. To investigate this problem, we transfect hippocampal neurons with BDNF-eGFP or TrkB-mCherry and separately plate them on two sides of a PDMS chamber. We look at 1) whether BDNF and TrkB are co-transported; 2) whether the transportation flux, speed and other features are affected by high frequency field stimulation. The results may help us to understand the mechanism under synaptic plasticity and memory formation.

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Increasing the Potassium Channel Density in Regularly Spiking Pyramidal Cells can Turn them into Fast Spiking
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The threshold dynamic of neurons can be classified into two main types: regular spiking neurons, showing a continuous frequency-stimulation current relationship and thus an arbitrarily low frequency at threshold current, and fast spiking neurons, showing a discontinuous relationship and a minimum frequency for repetitive firing. In a previous investigation of a hippocampal neuron model, we showed that the membrane density of critical ion channels is important for the bifurcation type and consequently for the threshold dynamics; it can cause the model to switch between fast and regular spiking. In the present study we extend our previous analysis with experimental tests, using the dynamic clamp technique. We injected currents, calculated from voltage clamp descriptions of potassium currents, into regularly spiking pyramidal cells, thereby altering their threshold dynamics to fast spiking. The results confirm the conclusion from the previous study that the type of threshold dynamics of neurons can critically depend on the channel density. Moreover, we show by analysing other well-described membrane models with techniques from nonlinear dynamical system theory how the channel density as bifurcation parameter is influenced by other parameters such as channel kinetics, in some cases reducing the threshold dynamics exclusively to fast spiking. In conclusion, the overall structure of the phase space around the stationary potentials must be taken into account when trying to understand the threshold dynamics of neurons, and, consequently, the global oscillatory activity of networks of neurons.

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A Computer Model Study of Tonic Spiking and Bursting in Thalamic Relay Neurons
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Thalamic relay neurons process visual signals from retina on the way to cortex, and seem to encode the information in dual modes: tonic spiking and bursting. The mode of firing depends critically on the history of membrane potential. For example, when the membrane rests at levels close to the firing threshold, relay neurons generate tonic spikes, but when the membrane is sufficiently hyperpolarized by IPSCs, they produce bursts. Therefore, it seems that the visual signal from retina to cortex is not only transferred but also transformed by thalamus. Studies have shown that the bursting mode can be attributed to the low-threshold T-type Ca^{2+} ion channels that are highly expressed in these neurons. We have developed a detailed model neuron, based on anatomically realistic models of Thalamic relay neurons, to examine the ionic mechanisms that are responsible for the dual mode firings both at the ion channel level and cellular level. Consistent with experimental data, we show that (1) when the membrane potential is close to the resting membrane potential, the model neuron fires tonic spikes; (2) when sufficiently hyperpolarized for about 100ms, the model neuron is able to fire bursts due to the deinactivation of T-type calcium channels that contribute the majority of the inter-burst current via slow deactivation. In addition, we investigate the effects of epilepsy-linked mutations in the neuronal Na^{+} channel and T-type Ca^{2+} channel on the dual mode of firing using experimentally based gating models. Our results demonstrate that sodium and T-type calcium channel mutations promote and accelerate tonic and burst firing.

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Models Of Paraventricular Nucleus (PVN) Sympathetic Neurone Modulation by Glucose and Hypoglycaemia
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Hypoglycaemia activates much of the sympathetic nervous system (Fagius 2003. Acta Physiol. Scand. 177:337-343) and this is likely to be important to glucose counter-regulation. The PVN is ideally suited to mediate this response since it contains a high density of spinally-projecting sympathetic control neurones. Furthermore, inactivation of the PVN with lignocaine blunts counter-regulation (Evans *et al.* 2003 Am. J. Physiol. 284:R57-65).
Our *in vitro* data show paradoxical responses of PVN sympathetic control neurones (SPNs) to hypoglycaemia: They express K_{ATP} channels and most are inhibited or unaffected by hypoglycaemia, whereas *in vivo* they appear to be activated by hypoglycaemia. There could be several possible explanations, however, in this study we explored the possibility that the paradox is accounted for by network properties in the PVN, and differential expression of K_{ATP} channels.
We constructed very simple Neuron (Hines & Carnevale 1997. Neural Comput. 9:1179-1209) models of SPNs with inputs from both excitatory ''Netstim'' neurones and inhibitory interneurones. The interneurones are also driven by excitatory ''Netstim'' neurones. Both interneurones and SPNs incorporate identical K_{ATP} channels, but the latter with a lower density. We modelled the situation where this network is intact (*in vivo*) and where the inhibitory interneurones were lost (*in vitro*).
In the *in vitro* model, SPN K_{ATP} conductance was sufficient for the expected (dose-related) decrease in action potential frequency with hypoglycaemia. Interestingly, however, with no changes to the set-up of the SPN neurones, but re-introduction of input from the inhibitory interneurones, the effect of hypoglycaemia was reversed. Hypoglycaemia now activated SPNs. This model also reproduced the common observation that whilst SPNs in brain slice experiments tend to be ''spontaneously'' active, they tend to be silent *in vivo*, but activated by $GABA_A$ inhibition.

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Effects of Cellular Adaptations to Partial Demyelination on Spike Patterns in a Model Axon
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In a computational model, axons undergoing demyelination can produce a wide variety of spike patterns ranging from conduction failure to high-frequency bursting. We have simulated cellular adaptations to partial demyelination to understand what an axon might gain from adaptations to changes in excitability. Observed clinical phenomena in multiple sclerosis include an increase in axon diameter and the aggregation of mitochondria during demyelination. We, therefore, examined the effect of axon diameter swelling and increased activity of Na-K pumps on axonal excitability. Increasing the diameter of a partially demyelinated axon by 2-fold (as has been observed in human cases) had the effect of increasing the ''safety factor'' for successfully conducting a single spike across a demyelinated patch by 37% uniformly across a wide range of ion channel densities. At the other end of pathological spike behavior range, the un-evoked burst-pattern threshold was unaffected by the girth doubling at physiologically relevant densities of ion channels. Only at unusually high densities was a lower burst-threshold observed (−43%). But another measure of burst activity was altered by cable swelling. In the control demyelinated axon the frequency of bursting followed an oscillating pattern that was dependent on membrane current density. This sinusoidal frequency-density relationship was nearly flattened, or damped, by axon swelling. We addressed mitochondrial accumulation by assuming this cellular adaptation would impact Na-K pump activity. We discovered that increasing the Na-K pump activity only in the demyelinated areas caused early termination of the un-evoked bursting behavior. Our results suggest new interpretations of previous clinical and electrophysiological observations related to axonal intrinsic excitability in demyelination diseases. NIMH R01MH079076 and HHMI.

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An Improved Curvilinear Gradient Method for Parameter Estimation in Complex Model Systems: Application to Gating of A Cardiac Ion Channel
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Since the seminal work of Hodgkin and Huxley1 describing a model of the neuronal action potential, there has been tremendous interest in the power of mathematical modeling in the field of ion channel research. However, as we learn more about the physiology of these molecules the models describing their